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EXAMINER
FORMAN, BETTY J

ART UNIT	PAPER NUMBER
1634	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/613,006	Applicant(s) SCHENA, MARK A.	
	Examiner BJ Forman	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 19 February 2002 has been entered.

This action is in response to papers filed 19 February 2002 in Paper No. 13 in which new claim 27 was added, the previous rejection was discussed and Formal Drawings and Declaration under 37 C.F.R. 1.132 were submitted. The previous rejections in the Office Action of Paper No. 8 dated 19 September 2001 are maintained. All of the arguments have been thoroughly reviewed and are discussed below. New grounds for rejection are discussed.

Currently claims 1 and 3-27 are under prosecution.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is indefinite for the recitations "CFTR" and "GALT" because the recitations are abbreviations the meaning of which may change over time. Therefore, the claim is indefinite

because one of skill in the art may not be appraised of the scope of the claim. It is suggested that the claim be amended to provide the full name of the genetic loci.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 8, 9, 12, 14, 17, 18, 21 and 24 are rejected under 35 U.S.C. 102(b) as anticipated by Lashkari et al. (Proc. Natl. Acad. Sci. USA, 1997, 94: 13057-13062).

Regarding Claim 1, Lashkari et al. disclose a method of simultaneously genotyping multiple samples, the method comprising: amplifying a plurality of genomic segments from a plurality of samples using a plurality of polymerase chain reaction primers, each genomic segment comprising a distinct genetic locus; forming a microarray on a surface form the amplified genomic segments wherein each location on the surface contains amplified material derived from a single sample and consisting essentially of a single genomic segment (page 13057, right column, first-third paragraphs); hybridizing the microarray with a mixture of labeled synthetic oligonucleotides (page 13058, left column, second paragraph), wherein the mixture comprises oligonucleotides complementary to the genomic segments; and deriving genotyping information simultaneously for plurality of samples at the plurality of genetic loci by detecting signals from the hybridized microarray to thereby genotype the multiple samples (page 13059, left column, last paragraph-right column).

Regarding Claim 8, Lashkari et al. disclose the method wherein the microarray comprises at least 1000 spots per square centimeter (page 13058, right column, first full paragraph).

Regarding Claim 9, Lashkari et al. disclose the method wherein the mixture of labeled synthetic oligonucleotides comprises ten different oligonucleotide sequences (page 13059, Table 1).

Regarding Claim 12, Lashkari et al. disclose the method wherein hybridizing is performed in an aqueous solution comprising salts and detergent (page 13058, left column third full paragraph).

Regarding Claim 14, Lashkari et al. disclose the method wherein the labeled synthetic oligonucleotides comprise fluorescent labels (page 13058, left column, second paragraph).

Regarding Claim 17, Lashkari et al. disclose the method wherein the signals are generated by fluorescence emission form the labeled synthetic oligonucleotides (page 13058, right column, lines 1-2).

Regarding Claim 18, Lashkari et al. disclose the method wherein the signals are generated by fluorescence emission at more than one wavelength of light (page 13058, right column, lines 1-2).

Regarding Claim 21, Lashkari et al. disclose the method wherein surface comprises glass (page 13058, right column, second full paragraph).

Regarding Claim 24, Lashkari et al. disclose the method wherein the microarray is formed by mechanical micro-spotting (page 13057, right column, last paragraph).

Response to Arguments

6. Applicant argues that one of skill in the art would understand that the claimed synthetic oligonucleotides refers exclusively to oligonucleotides which are chemically synthesized and because Lashkari et al does not teach or suggest a microarray hybridized with chemically synthesized oligonucleotides, they do not teach or suggest the claimed invention. The argument is not found persuasive for the reasons stated in the previous office action i.e. "synthetic" as defined by Academic Press Dictionary of Science and Technology (Morris, C. ed.

Academic Press, 1992, page 2157) generally is defined as meaning "any product or item that is the result of human technology rather than something that exists in nature". It is noted that the Academic Press Dictionary provides three definitions one of which is quoted above and is referred by the dictionary as an engineering definition. The **first** definition provided by the dictionary is referred to as the **science** definition which recites "relating to, produced by, or involving synthesis." The second definition provided by the dictionary is referred to as the chemistry definition which recites "relating to compounds formed artificially by chemical synthesis." Given the three similar definitions of "synthetic" provided, the labeled cDNA and the labeled genomic DNA both of which are produced by synthesis; both of which are the result of human technology; both of which do not exist in nature; and both of which are artificially formed are, according to standard scientific definitions and terminology, "synthetic". Therefore, the labeled cDNA and labeled genomic DNA of Lashkari et al. are encompassed by the claimed "synthetic oligonucleotides".

Applicant argues that the examiner "**constructs** a definition of ""synthetic oligonucleotide"" from a definition of ""synthetic"". The examiner acknowledges that a definition of synthetic oligonucleotides was derived from a dictionary definition of "synthetic".

Applicant argues that the definition of synthetic appropriate for chemistry ("relating to compounds formed artificially by chemical synthesis") constructed by juxtaposing the term oligonucleotide would be appropriate for synthetic oligonucleotide because oligonucleotides are chemical compounds. The argument has been considered but is not found persuasive because as stated above, standard definitions of "synthetic" juxtaposed with "oligonucleotides encompasses the cDNA and labeled genomic DNA of Lashkari et al. The claims are given the broadest reasonable interpretation consistent with the broad claim language and specification wherein "synthetic oligonucleotide" are not defined and are not limited to "chemically synthesized oligonucleotides". Therefore, given the broadest reasonable interpretation of the claims, the labeled cDNA and labeled genomic DNA of Lashkari et al. are encompassed by the claimed "synthetic oligonucleotides".

The courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); and *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111).

Claim Rejections - 35 USC § 102/103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 5, 8, 11, 12, 14, 17, 18, 21, 24 and 26 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Brown et al. (U.S. Patent No. 5,807,522, issued 15 September 1998).

Regarding Claim 1, Brown et al. disclose a method of simultaneously genotyping multiple samples, the method comprising: amplifying a plurality of genomic segments from a plurality of samples (i.e. a plurality of known genes derived from two cell types) using a plurality of polymerase chain reaction primers, each genomic segment comprising a distinct genetic locus; forming a microarray on a surface from the amplified genomic segments wherein each location on the surface contains amplified material derived from a single sample and consisting essentially of a single genomic segment; hybridizing the microarray with a mixture of labeled synthetic oligonucleotide i.e. cloned DNA fragments wherein the mixture comprises oligonucleotides complementary to the genomic segments; and deriving genotyping information simultaneously for plurality of samples at the plurality of genetic loci by detecting signals from the hybridized microarray to thereby genotype the multiple samples (Column 4, line 60-Column 5, line 8). The preceding rejection is based on judicial precedent following In re Fitzgerald, 205 USPQ 594 because Brown et al. is silent with regard to amplifying the plurality of genomic segments using a plurality of primers. However, the plurality of primers recited in Claim 1 is deemed to be inherent in the array of polynucleotides representing a plurality of known genes of Brown et al. because the polynucleotides representing the known genes would have been synthesized using a plurality of primers i.e. a set of primers for each known gene. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the

claimed invention was made to use a plurality of primers to obtain the polynucleotides representing a plurality of known genes for the known benefits of primer amplification i.e. selectively obtaining multiple copies of known sequences. The burden is on applicant to show that the claimed plurality of primers is either different or non-obvious over that of Brown et al.

Regarding Claim 5, Brown et al. teach the method where in the segments comprise multiple forms of mutated genes i.e. human disease loci (Column 14, lines 55-60)

Regarding Claim 8, Brown et al. disclose the method wherein the microarray comprises at least 1000 spots per square centimeter (Column 14, lines 19-21).

Regarding Claim 11, Brown et al. disclose the method wherein the genomic segments each comprise between about 40 and 1000 base pairs (Column 14, lines 31-34).

Regarding Claim 12, Brown et al. disclose the method wherein hybridizing is performed in an aqueous solution comprising salts and detergent (Column 16, lines 57-61).

Regarding Claim 14, Brown et al. disclose the method wherein the labeled synthetic oligonucleotides comprise fluorescent labels (Column 4, lines 55-59).

Regarding Claim 17, Brown et al. disclose the method wherein the signals are generated by fluorescence emission from the labeled synthetic oligonucleotides (Column 4, line 60-Column 5, line 8).

Regarding Claim 18, Brown et al. disclose the method wherein the signals are generated by fluorescence emission at more than one wavelength of light (Column 4, line 60-Column 5, line 6).

Regarding Claim 21, Brown et al. disclose the method wherein surface comprises glass (Column 13, lines 47-57).

Regarding Claim 24, Brown et al. disclose the method wherein the microarray is formed by mechanical micro-spotting (Column 3, lines 23-41).

Regarding Claim 26, Brown et al. teach a method of simultaneously genotyping multiple samples comprising: amplifying a genomic segment comprising a genetic locus from a plurality

of samples (i.e. all known mutations of a given gene wherein the plurality of mutations are inherently from a plurality of samples); forming a microarray on a surface from the amplified genomic segments wherein each location on the surface contains material derived from a single sample (i.e. a known mutation); hybridizing the microarray with a mixture of labeled synthetic oligonucleotides wherein the mixture comprises oligonucleotides complementary to the genomic segment; and deriving genotyping information for the plurality of samples simultaneously by detecting signals from the hybridized microarray to thereby genotype the multiple samples (Column 15, lines 19-43) but they do not specifically teach the genomic segments are amplified using polymerase chain reaction primers. However, the primers recited in Claim 1 is deemed to be inherent in the array of fragments representing all know mutations of a gene in the method of Brown et al. because the fragments representing the known mutations would have been synthesized using primers i.e. a set of primers for each known gene. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use primers to obtain the polynucleotides representing a plurality of known genes for the known benefits of primer amplification i.e. selectively obtaining multiple copies of known sequences. The burden is on applicant to show that the claimed plurality of primers is either different or non-obvious over that of Brown et al.

Response to Arguments

9. Applicant argues that because Brown et al do not teach or suggest hybridizing the microarray with a mixture of labeled synthetic oligonucleotides, they do not anticipate the invention. The argument has been considered but is not found persuasive for the reasons stated above i.e. the claims are given the broadest reasonable interpretation consistent with the broad claim language and specification wherein "synthetic oligonucleotide" are not defined and are not limited to "chemically synthesized oligonucleotides". Therefore, given the broadest reasonable interpretation of the claims, the labeled cDNA and labeled genomic DNA of Brown et al. are encompassed by the claimed "synthetic oligonucleotides".

The courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification *In re Morris*, 127 F.3d 1048, 1054-55,

44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); and *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111).

Claim Rejections - 35 USC § 103

10. Claims 3, 4, 6, 7, 9 and 10 are rejected under 35 U.S.C. 103(a) as obvious over Brown et al. (U.S. Patent No. 5,807,522, issued 15 September 1998).

Regarding Claims 3 and 4, Brown et al. teach a method of simultaneously genotyping multiple samples, the method comprising: amplifying a plurality of genomic segments from a plurality of samples (i.e. a plurality of known genes derived from two cell types) using a plurality of polymerase chain reaction primers, each genomic segment comprising a distinct genetic locus; forming a microarray on a surface from the amplified genomic segments wherein each location on the surface contains amplified material derived from a single sample and consisting essentially of a single genomic segment; hybridizing the microarray with a mixture of labeled synthetic oligonucleotide i.e. cloned DNA fragments wherein the mixture comprises oligonucleotides complementary to the genomic segments; and deriving genotyping information simultaneously for plurality of samples at the plurality of genetic loci by detecting signals from the hybridized microarray to thereby genotype the multiple samples (Column 4, line 60-Column 5, line 8) wherein the plurality of samples comprises two cell types and wherein the plurality of samples may be "many types of known pathogens" which clearly suggests at least 10 distinct samples and at least 5,000 distinct samples (Column 14, lines 63-67) but they do not specifically teach the samples comprise at least 10 distinct samples (Claim 3) or at least 5,000 distinct samples (Claim 4). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the "many pathogens" teaching of Brown

et al. to form a microarray suggested by Brown et al. (Column 14, lines 63-67) comprising amplified genomic segments from 10 or 5,000 samples to thereby provide a microarray comprising fragments from 10 samples for identifying subsets of pathogens i.e. bacterial pathogens for the expected benefit of rapid and convenient screening of bacterial pathogens as taught by Brown et al. (Column 15, lines 59-61). The skilled practitioner in the art would have been further motivated to provide a microarray comprising fragments from 5,000 distinct samples for identification of all known pathogens for the expected benefit of performing mass diagnostic screenings efficiently as taught by Brown et al. (Column 15, lines 59-64).

Regarding Claim 6, Brown et al. teach the method where in the segments comprise multiple forms of mutated genes (Column 14, lines 55-60) but they do not teach the samples are neonatal blood samples. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the diagnostic array comprising mutated genes as taught by Brown et al. to comprise multiple forms of genes from neonatal blood samples for the obvious benefits of prenatal diagnosis i.e. by detecting the presence of mutant genes in neonatal samples, the disease maybe prevented and/or treated as early as possible.

Regarding Claim 7, Brown et al. teach the method where in the segments comprise multiple forms of mutated genes (Column 14, lines 55-60) but they do not teach specific genetic loci. However, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the genetic diagnostic microarrays of Brown et al. to provide specific genetic loci e.g. β-globin, CFTR and GALT, to thereby provide microarrays for disease-specific diagnosis for the expected benefit of rapid diagnosis of clinically important diseases as taught by Brown et al. (Column 15, lines 59-67).

Regarding Claim 9, Brown et al. teach the method wherein the mixture of labeled synthetic oligonucleotides comprises multiple different sequences wherein the method is useful for numerous applications e.g. gene mapping, genetic diagnostics, pathogenic identification (Column 14, lines 49-67) but they do not specifically teach 10 different sequences. However, it

would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the suggested uses of the method taught by Brown et al. and to hybridize the microarray with 10 different sequences e.g. representing 10 different clinically important genomic sequences to thereby determine the presence or absence of the clinically important genomic sequence within a sample for the expected benefit of providing large scale medical diagnostics as taught by Brown et al. (Column 15, lines 52-67).

Regarding Claim 10, Brown et al. teach the labeled synthetic are complementary to immobilized versions of the genes and they teach the immobilized fragments are about 50 nucleotides in length (Column 14, lines 31-34 and 55-60) but they do not teach the labeled synthetic nucleotides are between about 10 and 30 nucleotides in length. It is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the about 50 base pair genomic segment teaching of Brown et al. and using routine experimentation derive and use labeled oligonucleotides of 10 to 30 nucleotides in length for the obvious benefit of optimizing experimental conditions to thereby maximize experimental results.

Response to Arguments

11. Applicant argues that the instant invention is not obvious over Brown et al because they do not teach or suggest hybridizing the microarray with a mixture of labeled synthetic oligonucleotides. The argument has been considered but is not found persuasive for the reasons stated above i.e. the claims are given the broadest reasonable interpretation consistent with the broad claim language and specification wherein "synthetic oligonucleotide" are not defined and are not limited to "chemically synthesized oligonucleotides". Therefore, given the broadest reasonable interpretation of the claims, the labeled cDNA and labeled genomic DNA of Brown et al. are encompassed by the claimed "synthetic oligonucleotides".

12. Claims 13, 15, 16 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (U.S. Patent No. 5,807,522, issued 15 September 1998) in view of Wang et al. (Science, 1998, 280: 1077-1082).

Regarding Claim 13, Brown et al. teach a method of simultaneously genotyping multiple samples, the method comprising: amplifying a plurality of genomic segments from a plurality of samples (i.e. a plurality of known genes derived from two cell types) using a plurality of polymerase chain reaction primers, each genomic segment comprising a distinct genetic locus; forming a microarray on a surface from the amplified genomic segments wherein each location on the surface contains amplified material derived from a single sample and consisting essentially of a single genomic segment; hybridizing the microarray with a mixture of labeled synthetic oligonucleotide i.e. cloned DNA fragments wherein the mixture comprises oligonucleotides complementary to the genomic segments; and deriving genotyping information simultaneously for plurality of samples at the plurality of genetic loci by detecting signals from the hybridized microarray to thereby genotype the multiple samples (Column 4, line 60-Column 5, line 8) but they do not teach the hybridization is performed at a temperature about 10° C below melting. However, Wang et al. teach a similar method of simultaneously genotyping multiple samples comprising amplifying genomic samples from a plurality of samples; forming a microarray on a surface and hybridizing the microarray with a mixture of synthetic oligonucleotides to thereby derive genotype information (page 1078, right column, first full paragraph) wherein hybridizing is performed at a temperature about 10 °C below the melting temperature of the synthetic oligonucleotides (page 1081, right column 16., last 7 lines and page 1082, left column, 25, lines 1-4). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the hybridization conditions of Wang et al. to the hybridization of Brown et al. and to hybridize the segments under stringent hybridization conditions to thereby specifically detect highly complementary hybrids for the

obvious benefits of accurately detecting hybrids and thereby accurately diagnosing clinically important hybridizations.

Regarding Claim 15, Brown et al. does not teach the labels are non-fluorescent. However, Wang et al. teach the similar method wherein the synthetic oligonucleotides comprise non-fluorescent labels i.e. biotin (page 1081, right column 16). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the fluorescent label of Brown et al. with the biotin label of Wang et al. for the known benefits of biotin-streptavidin labeling i.e. increased sensitivity of signal detection due to signal amplification from biotin-streptavidin binding.

Regarding Claim 16, Brown et al. do not teach the information distinguishes homozygous and heterozygous samples. However, Wang et al. teach the similar method wherein the genotyping information distinguishes sample from homozygotes and samples from heterozygotes at a specific genetic locus (page 1078, Table 1 and page 1082, 28). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the genotyping of Brown et al. with the homozygous/heterozygous distinction of Wang et al. for the expected benefit of characterizing genomic diversity at the nucleotide level and taught by Wang et al. (Abstract).

Regarding Claim 25, Brown et al. does not teach the labels are dendrimer labels. However, Wang et al. teach the similar method wherein the synthetic oligonucleotides comprise dendrimer labels i.e. biotin-streptavidin (page 1081, right column 16). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the fluorescent label of Brown et al. with the biotin label of Wang et al. for the known benefits of biotin-streptavidin labeling i.e. increased sensitivity of signal detection due to signal amplification from biotin-streptavidin binding.

Response to Arguments

13. Applicant argues that Wang et al do not remedy the defects of Brown et al and therefore the instant invention is not obvious over Brown et al and Wang et al. The argument

has been considered but is not found persuasive for the reasons stated above i.e. the claims are given the broadest reasonable interpretation consistent with the broad claim language and specification wherein "synthetic oligonucleotide" are not defined and are not limited to "chemically synthesized oligonucleotides". Therefore, given the broadest reasonable interpretation of the claims, the labeled cDNA and labeled genomic DNA of Brown et al. are encompassed by the claimed "synthetic oligonucleotides".

14. Claims 19-20 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (U.S. Patent No. 5,807,522, issued 15 September 1998) in view of Fodor et al. (U.S. Patent No. 5,800,992, filed 25 June 1996).

Regarding Claims 19-20, Brown et al. teach the method wherein the signals are generated by fluorescence emission at more than one wavelength (Column 17, lines 1-8) but they do not teach the emission after antibody staining. However, signals generated by fluorescence emission after antibody staining (Claim 19) and at more than one wavelength (Claim 20) was well known and routinely practiced in the art at the time the claimed invention was made as taught by Fodor et al. (Column 51, lines 50-57 and Column 52, lines 3-9). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the more than one fluorescence emission techniques of Brown et al. with the fluorescent emission after antibody staining as routinely practiced in the art based on available reagents and for the known benefits of antibody labeling i.e. commercially available and simple and therefore for the expected benefits of ease and economy.

Regarding Claims 22-23, Brown et al. teach the method comprising genomic segments, but they do not teach the genomic segments comprise amino linkers. However, Fodor et al. teach a similar method of genotyping samples comprising forming a microarray on a surface from oligonucleotide segments wherein the segments comprise amino linkers and the surface comprising aldehyde groups (Columns 63-64). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify genomic segments and

microarray surface of Brown et al. with the amino linkers and the surface comprising aldehyde groups to thereby attach the segments to the surface via specific activation and binding for the expected benefits of carefully controlled attachments and economy of reagents as taught by Fodor et al. (Column 68, lines 34-40).

Response to Arguments

15. Applicant argues that Fodor et al do not remedy the defects of Brown et al and therefore the instant invention is not obvious over Brown et al and Wang et al. The argument has been considered but is not found persuasive for the reasons stated above i.e. the claims are given the broadest reasonable interpretation consistent with the broad claim language and specification wherein "synthetic oligonucleotide" are not defined and are not limited to "chemically synthesized oligonucleotides". Therefore, given the broadest reasonable interpretation of the claims, the labeled cDNA and labeled genomic DNA of Brown et al. are encompassed by the claimed "synthetic oligonucleotides".

Response to Declaration filed under 35 C.F.R. 1.132

16. Ms. Foster states that "it is understood by those of ordinary skill that the term "synthetic oligonucleotide" refers exclusively to oligonucleotides prepared by chemical synthesis."..... "those of ordinary skill would not understand the term "synthetic oligonucleotide" to refer to oligonucleotides prepared by means other than chemical synthesis."... "those of ordinary skill in the chemical and biological sciences would not understand the term "synthetic oligonucleotide" to refer to oligonucleotides or oligomers made enzymatically.". Ms. Foster, referring to the definitions found in Academic Press Dictionary of Science and Technology cited by the examiner, states that juxtapositoning the chemical definition of "synthesis" would be equivalent to the meaning of "synthetic oligonucleotides" understood by those of ordinary skill in the chemical and biological sciences; juxtapositoning the engineering definition of "synthesis" would not be equivalent to the meaning of "synthetic oligonucleotides" understood by those of ordinary skill in the chemical and biological sciences; and juxtapositoning the science definition of "synthesis" would be equivalent to the meaning of "synthetic oligonucleotides" understood by those of ordinary skill in the chemical and biological sciences only if "synthesis were understood to refer to chemical synthesis".

Ms. Foster's comments have been considered but are not found persuasive because as Ms. Foster acknowledges, two of the three standard definitions provided by Academic Press

Dictionary of Science and Technology do not limit the definition of "synthetic" to chemically synthesized. Two of the three standard definitions define "synthetic" as much broader than chemical synthesis. Therefore, standard definitions of "synthetic" not limit the term "synthetic oligonucleotide" to chemically synthesized oligonucleotides.

Additionally, the comments are not found persuasive because the claims are given the broadest reasonable interpretation consistent with the broad claim language and specification wherein "synthetic oligonucleotide" are not defined and are not limited to "chemically synthesized oligonucleotides". Therefore, given the broadest reasonable interpretation of the claims, the labeled cDNA and labeled genomic DNA of Lashkari et al. are encompassed by the claimed "synthetic oligonucleotides".

The courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); and *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111).

NEW GROUNDS FOR REJECTION

17. The previous grounds for rejection, recited above, are maintained. New grounds for rejection are provided to further clarify the issues regarding patentability of the claimed subject matter.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

19. Claims 1, 3-5, 8-12, 14-17, 24, 26 and 27 are rejected under 35 U.S.C. 102(e) as being anticipated by Drmanac (U.S. Patent No. 6,025,136, filed 28 August 1998).

Regarding Claim 1, Drmanac discloses a method of simultaneously genotyping multiple samples comprising: amplifying a plurality of genomic fragments from a plurality of samples using a plurality of primers, each genomic segment comprising a distinct locus; forming a microarray on the surface from the amplified segments wherein each location on the surface contains amplified material derived from a single sample (Example 3, Column 5, line 37-Column 6, line 3); hybridizing the microarray with a mixture of labeled synthetic oligonucleotides wherein the mixture comprises oligonucleotides complementary to the genomic segments (Example 1, Column 5, lines 5-14); and deriving genotyping information simultaneously for the plurality of samples by detecting signals from the microarray (Example 6, Column 7, line 25-Column 8, line 46).

Regarding Claim 3, Drmanac discloses the method wherein the plurality of samples comprises at least 10 distinct samples i.e. a subarray contains a sample from each of 64 patients (Column 5, lines 59-60).

Regarding Claim 4, Drmanac discloses the method wherein the plurality of samples comprises at least 3200 distinct samples i.e. a subarray contains 256 samples (Column 4, lines 42-43) and the array comprises 50 subarrays (Column 3, lines .

Regarding Claim 5, Drmanac discloses the method wherein the genomic segments comprise human disease loci (Column 2, lines 7-12 and Column 8, lines 48-62).

Regarding Claim 8, Drmanac discloses the method wherein the surface of the microarray comprise at least 1000 locations per square centimeter i.e. 25/mm^2 (Column 5, lines 46-48).

Regarding Claim 9, Drmanac discloses the method wherein the labeled synthetic oligonucleotides comprise ten different oligonucleotide sequences (Column 4, line 59-Column 5, line 4 and Column 7, lines 29-44).

Regarding Claim 10, Drmanac discloses the method wherein the labeled synthetic oligonucleotides are between about 10 and 30 nucleotides in length (Column 4, line 59-Column 5, line 4).

Regarding Claim 11, Drmanac discloses the method wherein the genomic segments each comprise between about 40 and about 1000 base pairs (Column3, lines 27-34).

Regarding Claim 12, Drmanac discloses the method wherein hybridizing is performed in an aqueous solution comprising salts and detergent (Column 18, lines 17-30).

Regarding Claim 14, Drmanac discloses the method wherein the labeled synthetic oligonucleotides comprise fluorescent labels (Column 5, lines 5-13).

Regarding Claim 15, Drmanac discloses the method wherein the labeled synthetic oligonucleotides comprise non-fluorescent labels (Column 5, lines 5-13).

Regarding Claim 16, Drmanac disclose the method wherein the genotyping distinguishes homozygotes from heterozygotes (Column 4, lines 7-19).

Regarding Claim 17, Drmanac discloses the method wherein the labeled synthetic oligonucleotides comprise fluorescent labels (Column 5, lines 5-13) wherein the signals are generated by fluorescence emission form the labeled oligonucleotides (Column 7, lines 9-10).

Regarding Claim 24, Drmanac discloses the method wherein the microarray is formed by mechanical micro-spotting (Column 5, lines 40-48).

Regarding Claim 26, Drmanac discloses a method of simultaneously genotyping multiple samples comprising: amplifying a genomic segment comprising a genetic locus from a plurality of samples using polymerase chain reaction primers; forming a microarray on the surface from the amplified segments wherein each location on the surface contains material derived from a single sample (Example 3, Column 5, line 37-Column 6, line 3); hybridizing the microarray with a mixture of labeled synthetic oligonucleotides wherein the mixture comprises oligonucleotides complementary to the genomic segment (Example 1, Column 5, lines 5-14); and deriving genotyping information for the plurality of samples simultaneously by detecting signals from the microarray (Example 6, Column 7, line 25-Column 8, line 46).

Regarding Claim 27, Drmanac discloses a method of simultaneously genotyping multiple samples comprising: amplifying a plurality of genomic fragments from a plurality of samples using a plurality of primers, each genomic segment comprising a distinct locus; forming a microarray on the surface from the amplified genomic segments wherein each location on the surface contains amplified material derived from a single sample and comprising at least one genomic segment (Example 3, Column 5, line 37-Column 6, line 3); hybridizing the microarray with a mixture of labeled synthetic oligonucleotides wherein the mixture comprises oligonucleotides complementary to the genomic segments (Example 1, Column 5, lines 5-14); and deriving genotyping information simultaneously for the plurality of samples by detecting signals from the microarray (Example 6, Column 7, line 25-Column 8, line 46).

Claim Rejections - 35 USC § 103

20. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as obvious over Drmanac (U.S. Patent No. 6,025,136, filed 28 August 1997).

Regarding Claim 6, Drmanac teaches a method of simultaneously genotyping multiple samples comprising: amplifying a plurality of genomic fragments from a plurality of samples using a plurality of primers, each genomic segment comprising a distinct locus; forming a microarray on the surface from the amplified segments wherein each location on the surface contains amplified material derived from a single sample (Example 3, Column 5, line 37-Column 6, line 3); hybridizing the microarray with a mixture of labeled synthetic oligonucleotides wherein the mixture comprises oligonucleotides complementary to the genomic segments (Example 1, Column 5, lines 5-14); and deriving genotyping information simultaneously for the plurality of samples by detecting signals from the microarray (Example 6, Column 7, line 25-Column 8, line 46) wherein the samples are diagnostically important (Column 2, lines 7-12) but they do not teach the samples are neonatal blood samples. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the diagnostic array comprising mutated genes as taught by Drmanac to comprise multiple forms of genes from neonatal blood samples for the obvious benefits of prenatal diagnosis i.e. by detecting the presence of mutant genes in neonatal samples, the disease maybe prevented and/or treated as early as possible.

Regarding Claim 7, Drmanac teaches the method wherein the samples are diagnostically important (Column 2, lines 7-12) but they do not teach specific genetic loci. However, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the genetic diagnostic microarrays of Drmanac to provide specific genetic loci e.g. β-globin, CFTR and GALT, to thereby provide microarrays for disease-specific diagnosis for the expected benefit of rapid diagnosis of clinically important diseases as taught by Brown et al. (Column 15, lines 59-67).

21. Claims 13 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drmanac (U.S. Patent No. 6,025,136, filed 28 August 1997) in view of Wang et al. (Science, 1998, 280: 1077-1082).

Regarding Claim 13, Drmanac teaches a method of simultaneously genotyping multiple samples comprising: amplifying a plurality of genomic fragments from a plurality of samples using a plurality of primers, each genomic segment comprising a distinct locus; forming a microarray on the surface from the amplified segments wherein each location on the surface contains amplified material derived from a single sample (Example 3, Column 5, line 37-Column 6, line 3); hybridizing the microarray with a mixture of labeled synthetic oligonucleotides wherein the mixture comprises oligonucleotides complementary to the genomic segments (Example 1, Column 5, lines 5-14); and deriving genotyping information simultaneously for the plurality of samples by detecting signals from the microarray (Example 6, Column 7, line 25-Column 8, line 46) but they do not teach the hybridization is performed at a temperature about 10° C below melting. However, Wang et al. teach a similar method of simultaneously genotyping multiple samples comprising amplifying genomic samples from a plurality of samples; forming a microarray on a surface and hybridizing the microarray with a mixture of synthetic oligonucleotides to thereby derive genotype information (page 1078, right column, first full paragraph) wherein hybridizing is performed at a temperature about 10 °C below the melting temperature of the synthetic oligonucleotides (page 1081, right column 16., last 7 lines and page 1082, left column, 25, lines 1-4). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the hybridization conditions of Wang et al. to the hybridization of Drmanac and to hybridize the segments under stringent hybridization conditions to thereby specifically detect highly complementary hybrids for the obvious benefits of accurately detecting hybrids and thereby accurately diagnosing clinically important hybridizations.

Regarding Claim 25, Drmanac teaches the method wherein the labels are well known fluorescent labels (Column 5, lines 10-13) but he does not teach the labels are dendrimer labels. However, Wang et al. teach the similar method wherein the synthetic oligonucleotides comprise dendrimer labels i.e. biotin-streptavidin (page 1081, right column 16). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the fluorescent label of Drmanac with the biotin label of Wang et al. for the known benefits of biotin-streptavidin labeling i.e. increased sensitivity of signal detection due to signal amplification from biotin-streptavidin binding.

22. Claims 18-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drmanac (U.S. Patent No. 6,025,136, filed 28 August 1997) in view of Fodor et al. (U.S. Patent No. 5,800,992, filed 25 June 1996).

Regarding Claim 18, Drmanac teaches a method of simultaneously genotyping multiple samples comprising: amplifying a plurality of genomic fragments from a plurality of samples using a plurality of primers, each genomic segment comprising a distinct locus; forming a microarray on the surface from the amplified segments wherein each location on the surface contains amplified material derived from a single sample (Example 3, Column 5, line 37-Column 6, line 3); hybridizing the microarray with a mixture of labeled synthetic oligonucleotides wherein the mixture comprises oligonucleotides complementary to the genomic segments (Example 1, Column 5, lines 5-14); and deriving genotyping information simultaneously for the plurality of samples by detecting signals from the microarray (Example 6, Column 7, line 25-Column 8, line 46) but they do not teach signals are generated by more than one wavelength of light. However, Fodor et al teach a similar method wherein signals are generated by more than one wavelength and wherein the multiple wavelength signals permit

individual analysis of the genomic fragments (Column 52, lines 3-9). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the multiple fluorescent wavelength labels of Fodor et al to the multiple genomic fragment detection of Drmanac thereby permitting individual analysis of the fragments as taught by Fodor (Column 52, lines 3-9) for the expected benefit of facilitating the detection and analysis of multiple fragments on the array.

Regarding Claims 19-20, Drmanac teach the method wherein well known labels are utilized (Column 5, lines 5-13) but they do not teach signals are generated after antibody staining (Claim 19) and more than one wavelength after antibody staining (Claim 20). However, signals generated by fluorescence emission after antibody staining (Claim 19) and at more than one wavelength (Claim 20) was well known and routinely practiced in the art at the time the claimed invention was made as taught by Fodor et al. (Column 51, lines 50-57 and Column 52, lines 3-9). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the more than one fluorescence emission techniques of Drmanac with the fluorescent emission after antibody staining as routinely practiced in the art based on available reagents and for the known benefits of antibody labeling i.e. commercially available and simple and therefore for the expected benefits of ease and economy.

Regarding Claims 22-23, Drmanac teach the method comprising genomic segments (Column 5, lines 29-35), but they do not teach the genomic segments comprise amino linkers. However, Fodor et al. teach a similar method of genotyping samples comprising forming a microarray on a surface from oligonucleotide segments wherein the segments comprise amino linkers and the surface comprising aldehyde groups (Columns 63-64). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify genomic segments and microarray surface of Drmanac with the amino linkers and the surface comprising aldehyde groups to thereby attach the segments to the surface via specific

activation and binding for the expected benefits of carefully controlled attachments and economy of reagents as taught by Fodor et al. (Column 68, lines 34-40).

Conclusion

23. No claim is allowed.

24. The examiner's Art Unit has changed from 1655 to 1634. Please address future correspondence to Art Unit 1634.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
May 13, 2002